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Clopidogrel and Aspirin in Acute Ischemic Stroke and TIA:

Final Results of the POINT Trial

S. Claiborne Johnston,[1] J. Donald Easton,[2] Mary Farrant,[2] William Barsan,[3] Robin A. Conwit,[4] Jordan J. Elm,[5] Anthony S. Kim,[2] Anne S. Lindblad,[6] Yuko Y. Palesch,[5] and the Clinical Research Collaboration, NETT, and other POINT Investigators

[1]Dell Medical School, University of Texas, Austin, TX, USA; [2]Department of Neurology, University of California, San Francisco, CA, USA; [3]Department of Emergency Medicine, University of Michigan, Ann Arbor, MI, USA; [4]Division of Clinical Research, National Institute of Neurological Disorders, Bethesda, MD, USA; [5]Data Coordination Unit, Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC, USA; [6]The EMMES Corporation, Rockville, MD, USA.

Presenting Author

S. Claiborne Johnston, MD, PhD

The Dean's Office, Dell Medical School, University of Texas at Austin, TX, USA

Disclosures

- The study was funded by the US National Institute of Neurological Disorders and Stroke.
- Sanofi provided drug and placebo for 75% of subjects and reviewed a pre-final version of the manuscript.
- Dr. Johnston is receiving research support from AstraZeneca, the makers of ticagrelor.

Background

- The risk of stroke ranges from 3% to 15% in the 90 days following minor stroke and TIA.
- Clopidogrel and aspirin inhibit platelets synergistically.
- CHANCE found a 32% reduction in stroke risk over 90 days with clopidogrel-aspirin vs. aspirin.

Aims

- To compare clopidogrel (600 mg load followed by 75 mg/day) and aspirin (50-325 mg/day) to aspirin alone in reducing the risk of major ischemic events (ischemic stroke, MI, ischemic vascular death) during 90 days after acute minor stroke or TIA.
- To compare rates of major hemorrhage.

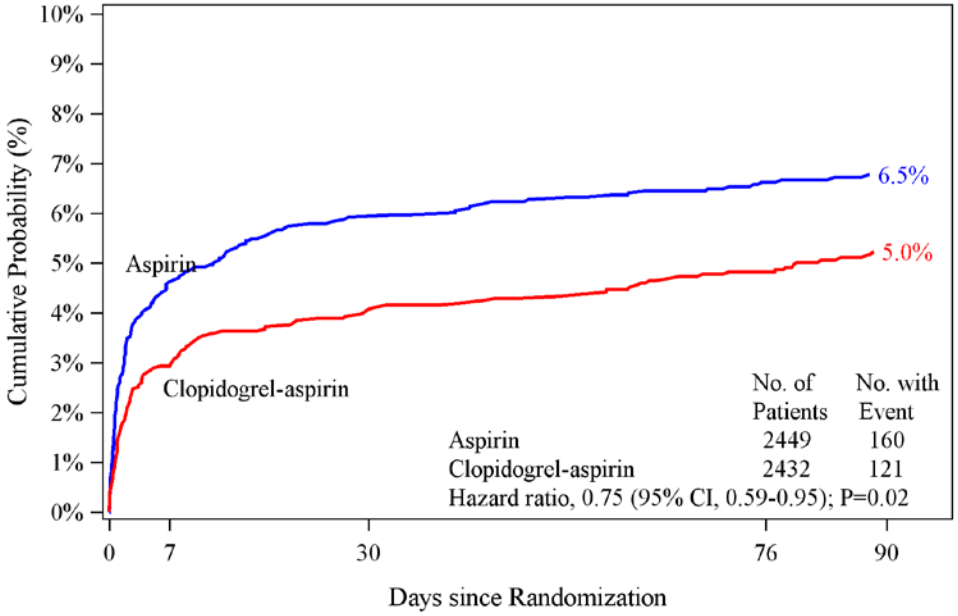
Key Inclusion Criteria

- Acute ischemic event:
  - Minor ischemic stroke (NIHSS $\leq$3), OR
  - High-risk TIA ($ABCD^2$ score $\geq$4)
- Randomized within 12 hours of event onset
- TIA symptoms not limited to numbness, visual changes, dizziness/vertigo.
- No receipt of thrombolysis or thrombectomy.
- No planned endarterectomy.
- No indication for anticoagulation, aspirin, or clopidogrel, and no contraindication for study drug.

Baseline Characteristics

Characteristic	Clopidogrel-Aspirin (N=2432)	Aspirin (N=2449)
Age (yr) - median (interquartile range)	65.0 (55.0-74.0)	65.0 (56.0-74.0)
Female sex– no. (%)	1097 (45.1%)	1098 (44.8%)
Race - no. (%)		
White	1774 (75.2%)	1781 (74.9%)
Black	473 (20.0%)	493 (20.7%)
Asian	77 (3.3%)	67 (2.8%)
Region - no. (%)		
United States	2014 (82.8%)	2029 (82.9%)
Outside United States	418 (17.2%)	420 (17.2%)
Taking aspirin at presentation – no. (%)	1417 (58.3%)	1397 (57.0%)
Time to randomization - no. (%)		
< 6h	755 (31.1%)	789 (32.2%)
≥ 6h	1676 (68.9%)	1660 (67.8%)
Qualifying event - no. (%)		
TIA	1056 (43.4%)	1052 (43.0%)
Ischemic stroke	1376 (56.6%)	1397 (57.0%)
Qualifying TIA baseline $ABCD^2$ score - median (IQR)	5.0 (4.0-6.0)	5.0 (4.0-5.0)
Qualifying ischemic stroke baseline NIHSS - median (IQR)	2.0 (1.0-2.0)	2.0 (1.0-2.0)

Results: Major Ischemic Events

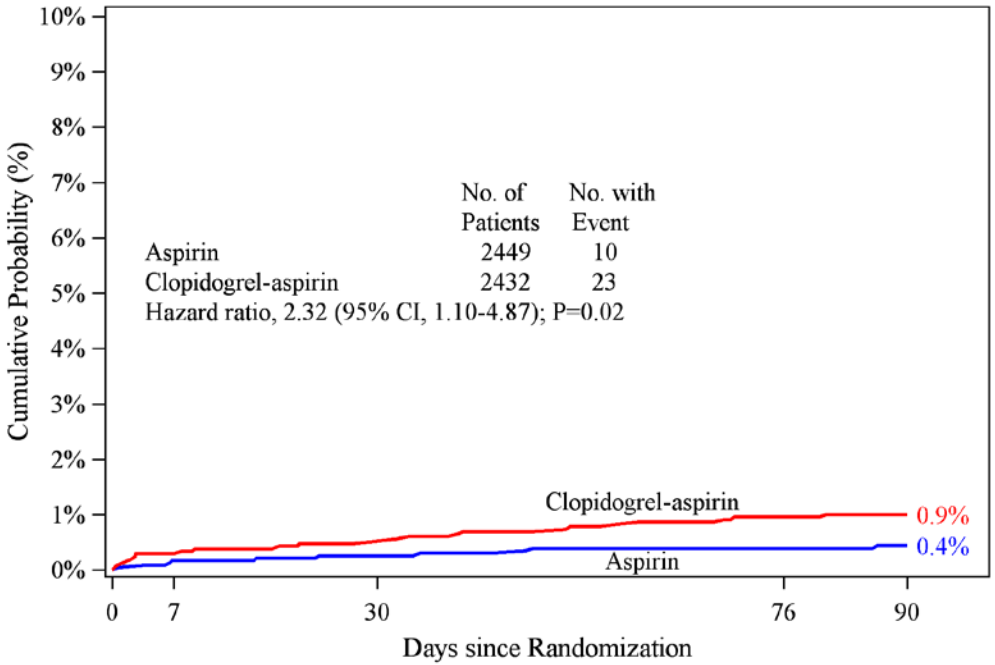


No. at Risk					
Aspirin	2449	2269	2153	2105	1365
Clopidogrel-aspirin	2432	2279	2179	2113	1445

Efficacy Outcomes

	Clopidogrel-Aspirin (N=2432)		Aspirin (N=2449)		Hazard Ratio (95% CI)	P Value
	Patients with Event no.	Event Rate %	Patients with Event no.	Event Rate %		
PRIMARY OUTCOME						
Ischemic stroke, MI, or ischemic vascular death	121	5.0	160	6.5	0.75 (0.59 - 0.95)	0.02
SECONDARY OUTCOMES						
Ischemic stroke	112	4.6	155	6.3	0.72 (0.56 - 0.92)	0.01
Myocardial infarction	10	0.4	7	0.3	1.44 (0.55 - 3.78)	0.46
Ischemic vascular death	6	0.2	4	0.2	1.51 (0.43 – 5.35)	0.52
Stroke (ischemic and hemorrhagic)	116	4.8	156	6.4	0.74 (0.58 - 0.94)	0.01
Composite of ischemic stroke, myocardial infarction, ischemic vascular death, or major hemorrhage	141	5.8	167	6.8	0.84 (0.67 - 1.05)	0.13

Results: Major Hemorrhage



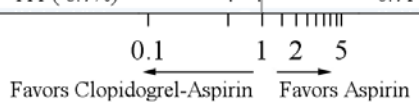
No. at Risk					
Aspirin	2449	2372	2271	2230	1448
Clopidogrel-aspirin	2432	2336	2257	2192	1505

Safety Outcomes

	Clopidogrel-Aspirin (N=2432)		Aspirin (N=2449)		Hazard Ratio (95% CI)	P Value
	Patients with Event no.	Event Rate %	Patients with Event no.	Event Rate %		
PRIMARY SAFETY OUTCOME						
Major hemorrhage	23	0.9	10	0.4	2.32 (1.10 – 4.87)	0.02
OTHER SAFETY OUTCOMES						
Hemorrhagic stroke	5	0.2	3	0.1	1.68 (0.40 - 7.03)	0.47
Symptomatic intracerebral hemorrhage	2	0.1	2	0.1	1.01 (0.14 - 7.14)	0.99
Other symptomatic intracranial hemorrhage	2	0.1	0	0		0.16
Major hemorrhage other than intracranial hemorrhage	17	0.7	7	0.3	2.45 (1.01 – 5.90)	0.04
Minor hemorrhage	40	1.6	13	0.5	3.12 (1.67 - 5.83)	<0.01

Primary Outcome by Subgroup

Subgroup	No. of patients	Clopidogrel-Aspirin no. of events (%)	Aspirin no. of events (%)	Hazard Ratio (95% CI)	Interaction P value
Overall	4881	121 (5.0%)	160 (6.5%)	0.75 (0.59, 0.95)	
Age (yr)					0.64
- <65	2426	57 (4.7%)	81 (6.6%)	0.71 (0.51, 1.00)	
- ≥ 65	2455	64 (5.2%)	79 (6.4%)	0.80 (0.57, 1.11)	
Sex					0.64
- Female	2195	53 (4.8%)	74 (6.7%)	0.71 (0.50, 1.01)	
- Male	2686	68 (5.1%)	86 (6.4%)	0.79 (0.58, 1.09)	
Race					0.32
- Asian	144	2 (2.6%)	3 (4.5%)	0.59 (0.10, 3.51)	
- Black	966	30 (6.3%)	52 (10.5%)	0.58 (0.37, 0.91)	
- White	3557	86 (4.8%)	97 (5.4%)	0.88 (0.66, 1.18)	
- Other	214	3 (2.8%)	8 (7.5%)	0.38 (0.10, 1.42)	
Region					0.89
- United States	4043	103 (5.1%)	137 (6.8%)	0.75 (0.58, 0.97)	
- Outside United States	838	18 (4.3%)	23 (5.5%)	0.78 (0.42, 1.45)	
Diagnosis of index event					0.46
- TIA	2108	43 (4.1%)	50 (4.8%)	0.85 (0.57, 1.28)	
- Minor stroke	2773	78 (5.7%)	110 (7.9%)	0.71 (0.53, 0.95)	
Time to randomization					0.49
- <6 hr	1544	40 (5.3%)	49 (6.2%)	0.85 (0.56, 1.29)	
- ≥ 6 hr	3336	81 (4.8%)	111 (6.7%)	0.71 (0.53, 0.95)	



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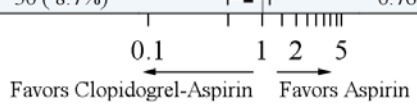
Overall	4881	121 (5.0%)	160 (6.5%)	0.75 (0.59, 0.95)	
Baseline NIHSS					0.66
- 0,1	1300	28 (4.4%)	46 (6.9%)	0.64 (0.40, 1.02)	
- 2,3	1444	48 (6.6%)	63 (8.8%)	0.73 (0.50, 1.06)	
ABCD2 score					0.08
- ≤ 5	1570	33 (4.2%)	31 (3.9%)	1.08 (0.66, 1.77)	
- > 5	535	10 (3.6%)	19 (7.4%)	0.48 (0.23, 1.04)	
Hypertension					0.74
- No	1487	25 (3.4%)	32 (4.2%)	0.80 (0.48, 1.36)	
- Yes	3373	95 (5.6%)	128 (7.6%)	0.73 (0.56, 0.95)	
Previous aspirin therapy					0.71
- No	2067	48 (4.7%)	62 (5.9%)	0.79 (0.55, 1.16)	
- Yes	2814	73 (5.2%)	98 (7.0%)	0.73 (0.54, 0.98)	
Previous statin therapy					0.73
- No	2993	77 (5.2%)	107 (7.0%)	0.73 (0.55, 0.98)	
- Yes	1888	44 (4.6%)	53 (5.7%)	0.80 (0.54, 1.19)	
Prevailing Aspirin dose					0.54
- 0 mg	193	7 (7.0%)	11 (11.8%)	0.54 (0.21, 1.39)	
- 1-81 mg	3012	61 (4.1%)	86 (5.7%)	0.70 (0.51, 0.97)	
- 82-100mg	423	12 (5.6%)	9 (4.3%)	1.30 (0.55, 3.08)	
- >100 mg	1131	37 (6.6%)	50 (8.7%)	0.76 (0.49, 1.15)	



Primary Outcome by Time Period

Time Period	Outcome	Clopidogrel-Aspirin (N=2432)			Aspirin (N=2449)		Hazard Ratio (95% CI)	P Value
		Subjects with Event no.	Event Rate %		Subjects with Event no.	Event Rate %		
0-30 days	Ischemic stroke, MI, or ischemic vascular death	96	3.9%		141	5.8%	0.73 (0.56 - 0.95)	0.02
	Major hemorrhage	12	0.5%		6	0.2%	2.07 (0.76 - 5.59)	0.15
31-90 days	Ischemic stroke, MI, or ischemic vascular death	25	1.0%		19	0.8%	1.30 (0.72 - 2.36)	0.39
	Major hemorrhage	11	0.5%		4	0.2%	2.77 (0.88 - 8.70)	0.08

Conclusion

- Clopidogrel-aspirin reduced risk of ischemic stroke, MI, and ischemic vascular death but increased risk of major hemorrhage compared to aspirin during 90-day treatment after acute minor ischemic stroke or TIA.
- For every 1000 patients treated, 15 major ischemic events would be prevented and 5 major hemorrhages would occur.

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ORIGINAL ARTICLE

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New Infarct (CT/MRI)					0.23
- No	3464	70 (4.1%)	83 (4.8%)	0.85 (0.62, 1.17)	
- Yes	1417	51 (7.2%)	77 (10.9%)	0.64 (0.45, 0.91)	
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